PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Juha-Matti SAVOLA et al.

Serial Number: 10/534,091 Group Art Unit: 1618

Filing Date: May 6, 2005 Examiner: Gembeh, Shirley V.

For: OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

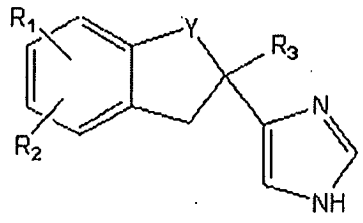
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Juha-Matti SAVOLA, hereby declare as follows:

1. I am one of the co-inventors of the invention disclosed and claimed in this application.

2. Claim 23 is the only independent claim, and defines a method of administering a formulation comprising as an active ingredient a substituted imidazole of formula (I)



(I)

where Y is $-CH_2-$ or $-CO-$, R_1 is halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, or an acid addition salt thereof, comprising

administering said formulation to a patient by oromucosal administration, wherein oromucosal administration is absorption via oral mucosa,

wherein the active ingredient is 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt.

3. The QT interval of an electrocardiogram (the time from the beginning of the QRS complex to the end of the T wave) is a measure of the duration of ventricular depolarization and repolarization. QT interval is an important cardiac safety assessment because of its association with delayed ventricular repolarization and consequent risks for fatal arrhythmia (including *torsade de pointes*). Much emphasis has been placed on the potential proarrhythmic effects of pharmaceuticals associated with QT interval prolongation. The U.S. FDA, among other competent

authorities, has issued guidance to the industry for its assessment[1].

4. On information and belief, the following work was performed by RCC Ltd., Itingen, Switzerland ("RCC"), an independent safety and toxicology laboratory, according to Good Laboratory Practice and principally by the same personnel.

4A. 4-Week oral toxicity (gavage) study in the dog[2] (JSN00-1007)

On information and belief, fipamezole [4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole] was orally administered (by gavage in water) at doses of 0 (water), 5 and 10 mg/kg/day[3] to 3 female and 3 male pure-bred beagle dogs per dose group for 4 weeks. Starting on Day 8, food was offered in two parts, the first before dosing

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[1] ICH S7B "Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" (November 2005).

[2]Of the available laboratory species, dogs have been found suitable for *in vivo* electrophysiology studies.

[3] The JSN00-1007 study also included a high dose group (15 mg/kg/day), but these data are not summarized here because of lack of comparative dose groups in the oromucosal delivery study (JSN00-1039).

and the second after dosing, due to the incidence of vomiting and low food consumption.

4B. 4-Week oromucosal (buccal) toxicity study in the dog (JSN00-1039)

On information and belief, fipamezole was administered by a spray device directly onto the buccal mucosa, at doses of 0 (spray vehicle), 5 and 10 mg/kg/day, in 3 female and 3 male pure-bred beagle dogs per dose group for 4 weeks.

4C. On information and belief, blood samples were obtained from all animals for plasma level determinations at 0.12, 0.25, 0.5, 1, 2, 4, 8 and 12 hours after dosing on Day 1 and Day 28. On each occasion approximately 4.5 ml of blood was drawn from the jugular vein and collected into blood collecting tubes containing lithium heparin. Following centrifugation plasma was transferred to polypropylene tubes and stored at -80 ± 10°C in the dark before transfer on dry ice to the bioanalytical laboratory for analysis by LC/MS/MS. Toxicokinetic data were analyzed using PK Solutions 2.0 for Excel software.

4D. Repeated dosing of fipamezole orally or oromucosally over 28 days at doses 5 or 10 mg/kg/day resulted in a 53-77% reduction in C_{max} concentrations (and subsequently also in AUC_{0-12} values) at the end of the treatment. See Table 1, attached. The oromucosal (buccal) route resulted in comparable systemic exposure as that after oral (gavage) route.

4E. On information and belief, standard toxicity parameters were assessed during these studies and histopathological evaluation was performed at the end of the treatment period:

- Following oral administration of fipamezole at doses of 5 mg/kg/day and 10 mg/kg/day for a period of 4 weeks, target organs included kidneys, liver and bile duct. See Table 1, attached. Tubular basophilia was recorded in the kidneys of several animals at 5 mg/kg/day or above. In the liver, hyaline hepatocellular inclusions were present in animals at 5 mg/kg/day or more, with the greatest severity at 5 mg/kg/day. Bile duct proliferation of minor severity was seen in the livers of some dogs from all treated groups. These findings were accompanied by hepatocellular hypertrophy in 2 of 6 animals at 5 mg/kg/day and 4 of 6 animals at 10 mg/kg/day. In addition, hepatocellular atrophy was recorded in

all males at 10 mg/kg/day. In serum, there was increase in gamma-glutamyl transferase in all the animals treated with fipamezole 10 mg/kg/day orally. In the group of the dogs receiving fipamezole 10 mg/kg/day orally, one of the male dogs had convulsions, which was a dose-limiting finding for further studies.

- There was no evidence of any systemic damage to target organs in the dogs which had fipamezole administered oromucosally. The only microscopic findings were seen at the site of application of the drug (*i.e.*, buccal mucosa), including some inflammatory changes possibly caused by an exaggerated pharmacological action of the test item on blood vessels. See Table 1, attached.

4F. On information and belief, electrocardiograms of each animal were recorded using standard ECG methods and a Multiscriptor EK 36 recorder (Hellige GmbH). During the 4-week treatment period records were made before and one hour after administration of fipamezole or its vehicle (water). Electrocardiograms were obtained using Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF) leads. The heart rate, P wave duration and amplitude and PQ, QRS and QT' intervals were measured using a representative section of the electrocardiogram from lead II. Of the ECG conductivity

intervals, the QT interval was corrected for the heart rate using the Van der Water's correction[4]: The values were calculated from the QT values reported in the tables converted into seconds. The results were converted to milliseconds for presentation.

- When fipamezole was orally administered, the mean pretest QTc intervals were 226 ± 4.05, 219 ± 3.44 and 222 ± 2.17 ms (n=6) for the groups starting to receive 0, 5 or 10 mg/kg fipamezole by oral administration.

- Oral administration of fipamezole (5 and 10 mg/kg/day for 28 days) prolonged the QTc interval from pretest values, by 14.0 ± 4.80 ms (p=0.0216) and 25.0 ± 3.99 ms (p=0.0003 when compared to that of the vehicle, -1.33 ± 2.95 ms) (n=6). In two-way analysis of variance for repeated measures, there was a statistically significant effect related to the treatment (F=3.74, p=0.0356), change over the 28-day treatment (F=20.21, p= 9.6×10^{-5}), and their interaction (F=7.47, p=0.00232). These changes in the QTc values are illustrated in Figure 1 (attached).

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[4] QTc = QT - 0.087 x [(60/HR) -1], where QT is the QT interval (seconds) and HR is heart rate (beats per minute); based on Spence et al., "The Heart Rate-Corrected Interval of Conscious Beagle Dogs: A Formula based on Analysis of Covariance," Toxicological Sciences, 45, 247-258 (1998).

- When fipamezole was oromucosally administered, the mean pretest QTc intervals were 234 ± 6.37, 234 ± 2.74 and 228 ± 2.93 ms (n=6) for the groups starting to receive 0, 5 or 10 mg/kg.

- Oromucosal administration of fipamezole (buccal doses of 5 and 10 mg/kg/day for 28 days) did not prolong the QTc interval from the pretest values. See Figure 2, attached.

- In conclusion, oral administration of fipamezole resulted in disturbances in cardiac conductivity. This effect was surprisingly not observed after oromucosal delivery, although the systemic exposure over the studied time period was comparable.

5. RCC performed another study to confirm the cardiac safety of fipamezole after oromucosal delivery in which four pure-bred beagle dogs were used for a telemetered conscious dog study according to the procedures of Good Laboratory Practice.

5A. On information and belief, the telemetry system (Data Sciences Inc., St. Paul, Minnesota, USA) consisted of an implantable transmitter unit (TL11 M2-D70-PCT) for the measurement of blood pressure, electrocardiogram and locomotor activity, a cage receiver (RMC-1), an ambient pressure monitor (APR-1), and a consolidation

matrix (OEM). A PC-based data acquisition system, Dataquest™ of Advanced Research Technology software, was used for data collection.

5B. On information and belief, each dog carried a transmitter which had been previously surgically implanted. After an acclimatization phase, the dogs were oromucosally administered with 0, 1, 5 and 15 mg/kg of fipamezole in the form of a buccal spray. Each of the four animals received four buccal doses with 5 - 15 days between each oromucosal administration. The doses were administered in a sequential manner to minimize side effects (salivation).

5C. On information and belief, electrocardiograms were recorded for at least 60 minutes before dosing and for at least 12 hours after dosing. Values obtained at -60, -30, 30 minutes, 1, 2, 3, 4 and 12 hours after dosing are reported. P-wave duration and amplitude, PQ, QRS and QT intervals were measured manually from the traces and reported. QT interval was corrected for heart rate (Van der Water's correction) to derive the QTc interval.

- The mean pretest QTc values were 254 ± 3.7, 257 ± 4.5, 244 ± 2.8 and 247 ± 2.55 ms (n=4) before dosing with fipamezole 0, 1, 5 or 15 mg/kg as oromucosal spray.

- No effects on absolute values for the QTc interval were seen at any dose of fipamezole tested (Figure 3).

- As can be seen from Figure 3, during the 1st hour after fipamezole dosing when the plasma levels of the compound are highest, as exemplified by Figure 4, there was no QTc prolongation.

6. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Signed this 15th day of January, 2009.

Juha-Matti Savola

Table 1. Summary of the toxicokinetic and toxicological data on the exposure of the dogs (n=6) with 4-week dosing of fipamezole by an oral or oromucosal buccal route.

Route	Dose	C_{max} (ng/ml)	AUC_{0-12} (ng/ml*h)	Target organs and findings
ORAL	5 mg/kg/day	Day 1: 2,020 ± 205 Day 28: 948 ± 59	Day 1: 6,751 ± 722 Day 28: 3,635 ± 404	Kidney: Tubular basophilia Liver: Hyaline hepatocellular inclusions, bile duct proliferation, hepatocellular hypertrophy
	10 mg/kg/day	Day 1: 3,141 ± 480 Day 28: 1,766 ± 206	Day 1: 12,298 ± 1,647 Day 28: 10,108 ± 1,685	CNS: Convulsions Kidney: Tubular basophilia Liver: Hyaline hepatocellular inclusions, bile duct proliferation, hepatocellular hypertrophy, hepatocellular atrophy; increase in gamma-glutamyl transferase. Bile duct: Degeneration of gall bladder mucosa
BUCCAL	5 mg/kg/day	Day 1: 2,562 ± 210 Day 28: 793 ± 146	Day 1: 3,921 ± 450 Day 28: 1,398 ± 206	Slight epithelial hyperplasia of buccal mucosa (site of administration).
	10 mg/kg/day	Day 1: 5,545 ± 914 Day 28: 1,269 ± 517	Day 1: 9,317 ± 1,516 Day 28: 3,346 ± 1,281	Slight epithelial hyperplasia with slight hyperkeratosis of buccal mucosa (site of administration).

Figure 1

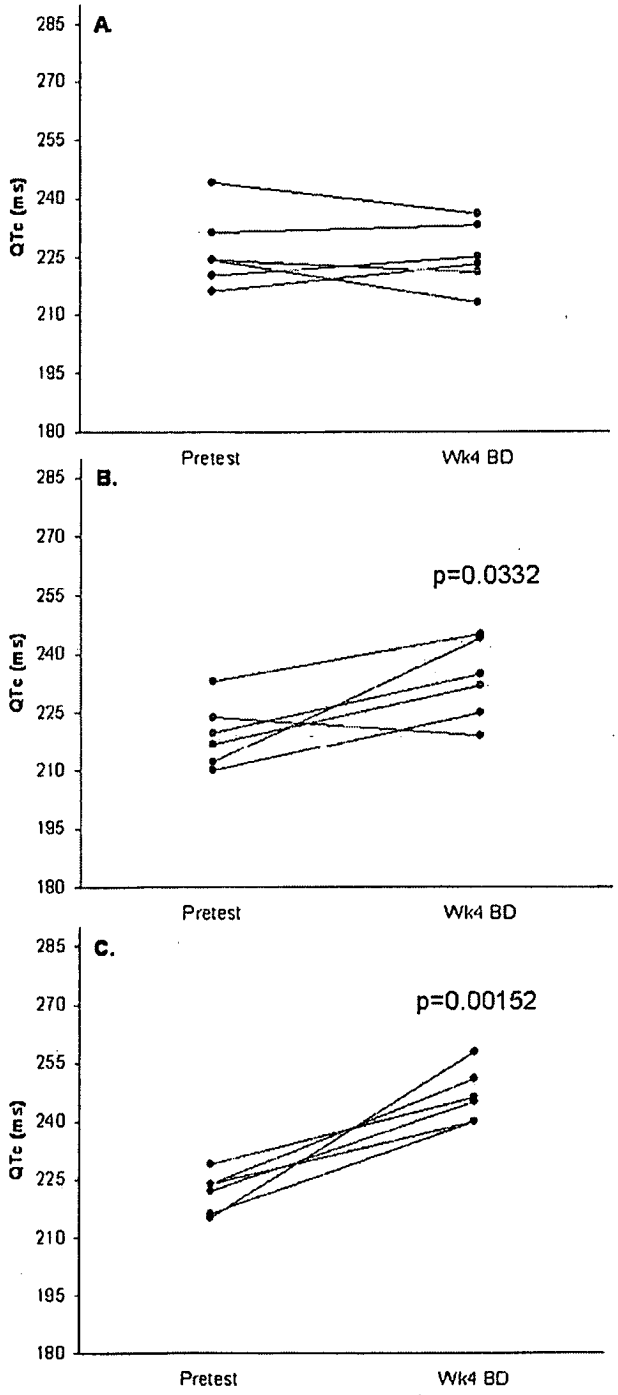

Figure 1. The QT intervals of cardiac conductivity, corrected for the heart rate using Van der Water's correction, in the 3 male and 3 female dogs, after 28-day daily oral dosing of fipamezole 0 (A), 5 (B) or 10 mg/kg (C). Pretest, QTc values before any study drug administration; Wk4 BD, QTc values on day 29, after 4-week daily dosing of the study drug. The p values refer to the p-values from two-sided paired student t test.

Figure 2

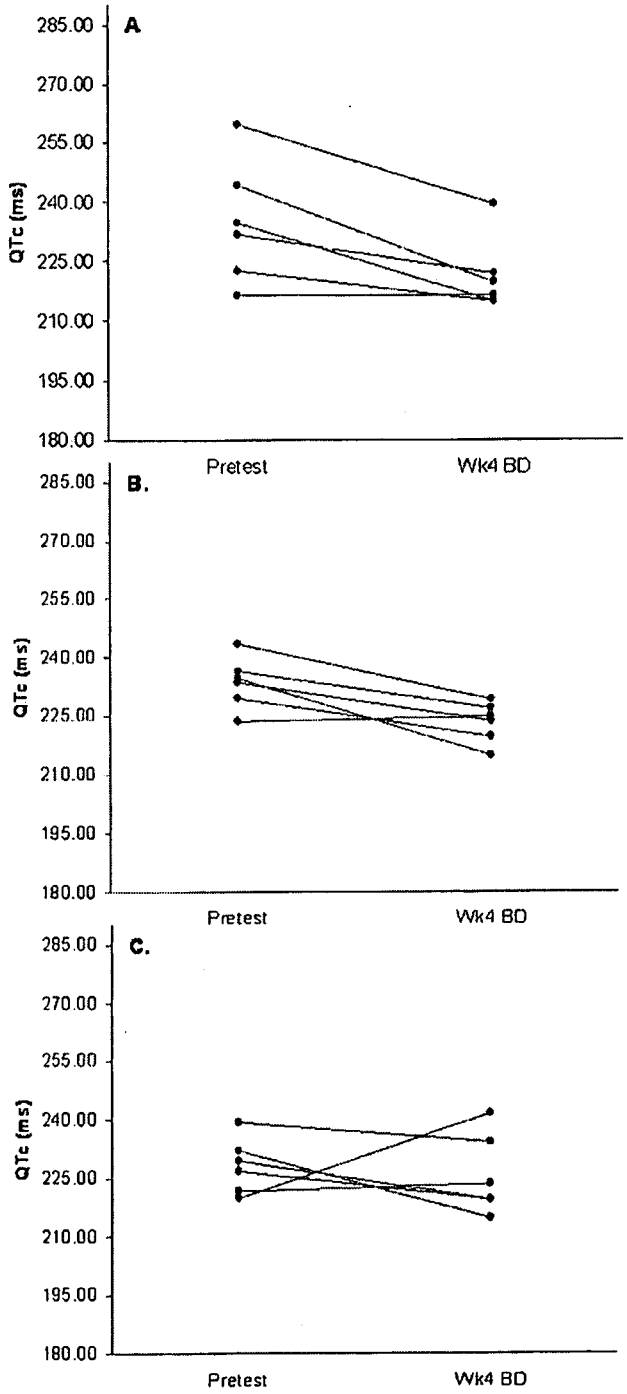

Figure 2. The QT intervals of cardiac conductivity, corrected for the heart rate using Van der Water's correction, in the 3 male and 3 female dogs, after 28-day daily buccal dosing of fipamezole 0 (A), 5 (B) or 10 mg/kg (C). Pretest, QTc values before any study drug administration; Wk4 BD, QTc values on day 29, after 4-week daily dosing of the study drug.

Figure 3

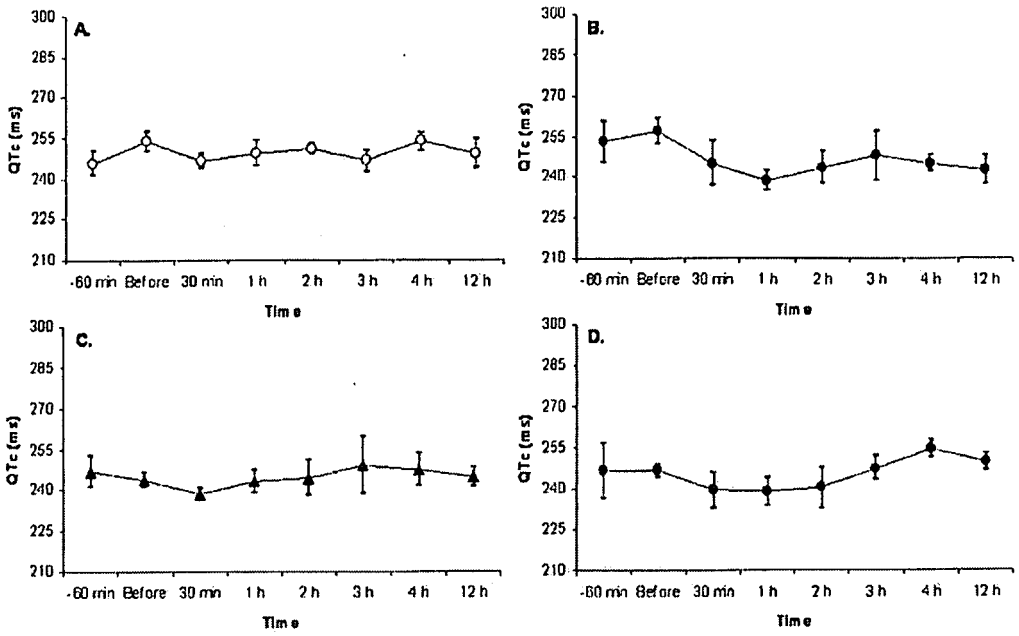

Figure 3. The QT intervals of cardiac conductivity, corrected for the heart rate using Van der Water's correction, in four beagle dogs, after buccal administration of fipamezole at concentrations of 0 (A), 1 (B), 5 (C) or 10 mg/kg (D).

Fig. 4

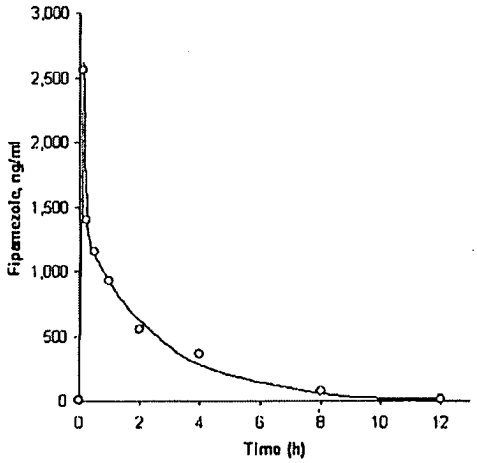

Figure 4. Plasma levels of fipamezole after oromucosal (buccal) dosing of 5 mg/kg in the dog.